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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/830,703	04/26/2001	Hermann Lubbert	STERN 1.001APC	1875

20995 7590 01/28/2003

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EXAMINER	
QIAN, CELINE X	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 01/28/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/830,703	LUBBERT, HERMANN	
	Examiner	Art Unit	
	Celine X Qian	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-8,13-15,17,18,20 and 22-32* is/are pending in the application.

4a) Of the above claim(s) *1,3-7,13,17,18,20,23-28 and 30-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8,14,15,22 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1, 3-8, 13-15, 17, 18, 20 and 22-32 are pending in the application.

Election/Restrictions

Applicant's election with traverse of Group III in Paper No. 12 is acknowledged. Applicant requests rejoinder of Groups IV and V (claims 17, 18, 20, 30 and 32). In addition, Applicant requests considering the claims in Groups IV and V upon the allowance of claim 8. Such request is granted.

Accordingly, claims 1, 3-7, 13, 17, 18, 20, 23-28, 30-32 are withdrawn from consideration for being directed to non-elected subject matter. Claims 8, 14, 15, 22 and 29 are currently under examination.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Specification

This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Claim Rejections - 35 USC § 101

Claim 14 is rejected under 35 U.S.C. 101 because it is not directed to statutory subject matter. It is PTO policy not to issue claims that encompass humans (see 1077 OG 24, April 21, 1987). This rejection may be overcome by inserting "non-human" before "animal".

Claim 22 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The descendent of the transgenic animal may be a normal animal, which is a product of nature. Therefore, the invention is unpatentable.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8, 14, 15, 22 and 29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the relative skill of those in the art; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue" (MPEP 2164.01 (a)).

The nature of the invention is a transgenic non-human mammal whose genome comprises an isolated or purified polynucleotide encoding a mutant mouse parkin2 protein, wherein the

transgenic non-human mammal displays symptoms of Parkinson's disease. The claims are further drawn to a method of making said transgenic non-human animal.

The breadth of claims is very broad. In the instant case, claims are drawn to a transgenic non-human mammal containing a mutant mouse parkin2 gene which produces less, less active or no parkin2 protein (see page 9). The claims encompass any transgenic non-human mammal containing any type of mutation or deletion in endogenous parkin2 gene or a foreign parkin2 transgene. In addition, the claims also encompass a transgenic non-human mammal containing a homolog of a mutant parkin2 gene. Further, claim 14 encompasses the method of generating a transgenic non-human animal comprising any mutant parkin2 transgene or a homolog, and a parkin2 knockout out non-human mammal.

The amount of guidance and working example in the specification is limited. The specification only teaches a method to make a transgenic parkin2 knockout mouse having exon3 deletion. However, the specification fails to teach whether this transgenic parkin2 knockout mouse exhibits phenotypes that are symptoms of Parkinson's disease. The specification also fails to disclose whether transgenic mouse or non-human mammals comprising other types of mutant parkin2 would exhibit symptoms of Parkinson's disease. The specification does not teach any mutant parkin2 homolog that would cause symptoms in Parkinson's disease either. Thus, the specification does not provide an enabling disclosure to make said transgenic non-human mammal which exhibits symptoms of Parkinson's disease. Without teaching from the specification, one skilled in the art would have to turn to prior art for guidance to make and use the transgenic mammal as claimed.

State of the Art, Predictability or Unpredictability of the art, Amount of experimentation necessary and Skill level of the artisan: When considering the predictability of this invention, one has to remember that many of the phenotypes examined in transgenic and knockout models are influenced by the genetic background in which they are studied and the effect of allelic variation and the interaction between the allelic variants (pg.1425, paragraph 1 in Sigmund, C.D. 2000. Arterioscler Thromb Vasc Biol.20:1425-1429). The specification does not disclose any phenotype of the parkin2 knockout mouse. Although the art teaches mutations in parkin2 gene linked to certain type of Parkinson's disease, whether the transgenic knockout mouse exhibits Parkinson's symptoms is unpredictable because it is unclear whether a parkin2 mutation alone is sufficient to cause Parkinson's disease. In addition, the claims encompass heterozygotes, but since heterozygotes have one functional allele, the heterozygotes would not be expected to have the same phenotype as the homozygotes. Thus, the phenotype of a mutant parkin2 transgenic or a parkin2 knockout animal is unpredictable. The specification, in the instant case, is not enabling for transgenic and/or knock out animals that exhibit no phenotype or that exhibit transgene-dependent phenotypes other than that of symptoms of Parkinson's disease. In addition, the transgene expression and the physiological consequences of transgene products are not always accurately predicted in transgenic mouse studies (pg.62, paragraph 1, lines 7-9 in Wall, R.J. 1996. Theriogenology 45:57-68). The particular genetic elements required for optimal expression varies from species to species. Our lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior (Wall, 1996). Therefore, in the absence of specific guidance and working examples, the production of transgenic non-human mammals with Parkinson's symptoms is unpredictable.

The specification fails to provide an enabling disclosure for the generation of other species of transgenic knockout non-human mammals besides mice having a disruption in the parkin2 gene because the guidance offered in the specification is limited to the generation of mice harboring such mutations and no teachings or guidance are offered with regard to how one would generate any other type of animal. Since homologous recombination is required for gene targeting methods such as employed in the instant invention, embryonic stem (ES) cells must be available to carry out the method. The only species in which the ES is available is the mouse (see e.g. Bradley et al., paragraph bridging pages 537-538). Campbell and Wilmut, 1997 acknowledge reports of ES-like cell lines in a number of species, but emphasize that as yet there are no reports of any cell lines which contribute to the germ line in any species other than the mouse (p.65). Likewise, Mullins et al. (1996, Clin. Invest. Vol 97, no. 7, 1557-1560) teach that "although to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated. This remains a major goal for the future and may well require the use of novel strategies which depart widely from the traditional methods used in the mouse" (p.1558, column 2, paragraph 1). Therefore, no knockout animals can be made for any species other than the mouse at the time of filing. As such, the method of making a transgenic parkin2 knockout non-human mammal is only enabled for a mouse, but not mammals of other species.

In view of the limited guidance in the specification and the unpredictability of the art, one skilled in the art would have to engage in undue experimentation overcome the problems as discussed above. Therefore, the invention is not enabled as claimed.

Claims 8, 15, 22 and 29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The written description requirement is set forth by 35 U.S.C. 112, first paragraph which states that the: "*specification* shall contain a written description of the invention. . .[emphasis added]." The written description requirement has been well established and characterized in the case law. A specification must convey to one of skill in the art that "as of the filing date sought, [the inventor] was in possession of the invention." See *Vas Cath v. Mahurkar* 935 F.2d 1555, 1560 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). Applicant may show that he is in "possession" of the invention claimed by describing the invention with all of its claimed limitations "by such descriptive means as words, structures, figures, diagrams, formulas, etc., that fully set forth the claimed invention." See *Lockwood v. American Airlines Inc.* 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

In analyzing whether the written description requirement is met, it is first determined whether the whether a representative number of species have been described by their complete structure. Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. The claims recite a homolog of mutant mouse parkin2 gene that causes symptoms of Parkinson's disease. The specification only discloses mutations in human parkin2 gene that are linked to Parkinson's disease. The specification fails to disclose any mutant mouse parkin2 gene that causes symptoms of Parkinson's disease. The specification fails to describe a mutant mouse parkin2 having same

mutation(s) as the human gene would cause symptoms of Parkinson's disease. As such, the structural and functional relationship between the mutant protein and its ability to cause Parkinson's disease is missing. Therefore, the specification fails to describe the invention in such a way to convey one skilled in the art that the inventors had possession of the invention at the time of filing.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8, 14, 15, 22 and 29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 8, 15, 22 and 29, the recitation of "...a mutant parkin2 protein...wherein said mutant causes symptoms of Parkinson's disease" renders the claims indefinite because it is unclear whether the mutant parkin2 cause Parkinson's disease in the transgenic non-human mammal or other non transgenic systems, for example, cells expressing the mutant parkin2 *in vitro*. As such, the metes and bounds of the claim cannot be established.

Regarding claim 22, the term "said animal" renders the claim indefinite because the term should refer to the descendant of the transgenic animal. It appears to refer to the transgenic animal of claim 8. Appropriate correction is required.

Claim 14 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: How the pseudopregnant female animal produces the transgenic animal comprising a mutant Parkin2 gene.

Claims 22 and 29 recites the limitation "transgenic animal" or "animal" in line. There is insufficient antecedent basis for this limitation in the claim. The parent claim (8) recites "transgenic non-human mammal" but not "transgenic animal" or "animal."

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 22 is rejected under 35 U.S.C. 102(b) as being anticipated by Allet et al. (1996, Journal of Cell Biology, Vol.135, No.2, 479-486, abstract).

Claim 22 is a product by process claim which reads on the product, the descendant of the transgenic animal.

Allet t al. disclose a wild type mouse (see abstract, line 1). Therefore, Allet et al. disclose the instantly claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Celine Qian, Ph.D.
January 26, 2003

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER